ADIPOSIS DOLOROSA.

A CLINICAL AND PATHOLOGICAL STUDY, WITH THE REPORT OF TWO CASES WITH NECROPSY.

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The number of cases of adiposis dolorosa that have been recorded with postmortem findings is so few that the following should be of interest:

Case I.—M. F., a housewife, white, aged fifty-seven years, a native of Philadelphia, was admitted to the alcoholic ward of the Philadelphia General Hospital, November 11, 1907, under the care of Dr. Mills; subsequently she was transferred to the service of Dr. Dercum. When admitted she was in a semistuporous condition, with a temperature of 97°; pulse, 110; respirations, 30. Her father and one brother died of consumption, her mother died of "general debility," and one brother became insane. She had the diseases of childhood, rheumatism in her wrists and knees upon several occasions, and "typhoid pneumonia" in 1876. She married when thirty-six years of age, but never became pregnant. Previous to her present illness she used alcohol in moderation, but since then has been taking a couple of "drinks" daily, to relieve her pain. She never was addicted to the use of any drug. For the past ten or twelve years she had been complaining of pain in her stomach at times, and since March, 1907, of severe pain and vomiting. On several occasions she vomited blood and passed blood from the bowels. For some time she has been very tender in the extremities, and for the past few weeks has been confused or delirious.

On examination she was a very corpulent elderly woman, with gray hair and no paralyses. The movements of the eyes could not be tested on account of the patient's condition, but they appeared normal, the pupils being equal, semicontracted, and reacting to light. The tongue was heavily coated, and without tremor. The pulse was rapid, irregular, intermittent, of small volume and low tension. The chest was well formed, the excursion good; the breasts were pendulous. The abdomen was markedly adipose; the skin of the abdomen and chest was smooth and elastic, while that over the legs was rough and dry. Marked tenderness was present all over the body, which did not seem to be limited to the course of the large nerves. Picking up some of the skin caused an outcry of pain, and touching any part of the body (except the face) caused an outcry of pain also. The outlines of the heart were increased downward and to the left and the right; no thrills were detected.

There was a systolic murmur at the aortic area, transmitted into the neck, with accentuation of the second pulmonic and aortic sounds. The breath sounds and pulmonary resonance were normal. The liver dulness extended from the fifth to the eighth interspaces in the mid-clavicular line; the spleen was not palpable but was slightly enlarged to percussion. There were two large bed sores, one on each buttock; another on the outer side of the left thigh. The biceps, triceps, knee, and Achilles reflexes were all absent. The styloid processes of the ulnæ were unusually prominent, a distinct sense of grating being felt in each wrist-joint, more especially in the right.

On November 13, 1907, a bulla about one and one-half inches long and one-half inch wide was present on the internal aspect of the left leg at the junction of the lower and middle third.

On November 14 two more bullæ were present, circular in shape, and about one inch in diameter, one being over the left knee and the other on the inner surface of the leg below the right knee. The urine was alkaline in reaction; had a specific gravity of 1020; contained no albumin and no casts, but did contain many triple phosphate crystals, many epithelial cells, and numerous leukocytes.

On November 17 three more bullæ were observed, a large one on the right heel and a small one at the junction of the metacarpophalangeal joint of each great toe.

On November 18 both albumin and casts were present in the urine.

The stupor gradually deepened, the heart weakened, the lungs became œdematous, and death occurred on November 21, 1907.

Autopsy. The findings were as follows: Fatty infiltration and degeneration of the heart; bilateral emphysema, with atelectasis of the lower lobe of the right lung; chronic diffuse nephritis; slight fatty infiltration of the liver. The subcutaneous fat in the region of the umbilicus was 6.5 cm. in thickness.

Specimens removed for examination were the brain and spinal cord, hypophysis, thyroid gland, adrenal glands, ovaries, and a portion of the subcutaneous fat containing small vessels and nerves.

Sections from the brain and cord were examined microscopically by the usual methods, but did not show any particular changes.

The thyroid gland was normal in size, but presented a marked difference between the lobes—the right lobe being distinctly harder than the left. Microscopically the right lobe showed a marked increase of the connective tissue at the expense of the parenchyma. Many of the acini were very small, the rest being about normal. In the left lobe, the acini were increased in size, many being enormously enlarged. Papillomatous ingrowths or plications, such as were found in a case reported by Dercum, were not observed. In both lobes, but especially in the right, were many areas of round-cell infiltration, not infrequently filling several adjacent acini. A few small hemorrhagic areas were also observed. The hypophysis was normal macroscopically, but under the microscope, sections stained with hematoxylin and eosin, and hematoxylin and Van Giesen's stain showed areas of round-cell infiltration in the glandular portion. Many cells were degenerated and without nuclei. In the nervous tissue of the posterior lobe were found glandular cells of the same character as those of the anterior lobe, irregularly arranged without any enveloping connective tissue, and being completely surrounded by the neuroglia. This singular condition has been described by Berckley, who claims to have found it in normal hypophyses. I have not seen this arrangement, however, in the sections obtained from any normal pituitaries that I have been able to examine. The adrenal glands presented no abnormalities, except certain irregularities in staining. The ovaries presented marked sclerosis. The fat showed the normal histological appearance, but the nerve filaments presented both interstitial and parenchymatous inflammatory changes.

CASE II.—M. W., a female, white, aged forty-eight years, a nurse, was admitted to the medical wards of the Philadelphia General Hospital, September 30, 1903, under the care of Dr. Salinger. On admission she complained of pain in the right foot so severe that she was disabled and could not stand; the right foot was swollen. There was severe pain in the occipital region extending over to the forehead. There was photophobia in both eyes and lacrymation, especially in the right. On the second day of admission she had a severe attack of herpes labialis.

Her maternal grandfather died at the age of eighty-six years, of old age. He was a small sized man. The grandmother died at eighty-four, following a dislocation of the hip. She was a fairly tall woman and very fat, the fat being equally distributed. The patient had five uncles on her mother's side, all of whom were tall and very stout, and three maternal aunts, one of whom was a very stout woman, dying at the age of forty-seven. During the last ten years of her life the latter complained greatly of pains in her legs, which were relieved by massage. Another aunt died at fifty years of cancer of the breast; she was tall and slender. The third aunt is living, is an undersized woman, not stout, and about sixty years of age. The mother of the patient was five feet, four inches tall, very thin and always complained of rheumatism and neuralgia, and died at forty-two from paralysis. The patient states that all of her cousins on her mother's side are large and stout people, but knows little more of them than this. Her father, who is the only known member on the paternal side, was a healthy man up to five years before his death; he died at seventy-six. His right leg was larger than the left, and was very painful. The patient's mother married at twenty-three, had six children, and one miscarriage. Two of the patient's brothers died of accidents. Another died from typhopneumonia at twenty-two, and a sister died of scarlet fever. The remaining brother is living, is very large, and suffers from rheumatism.

The patient has always been large. She had scarlet fever and chickenpox in childhood. She began to menstruate at fourteen; has always been regular. She had grippe in 1888, and made a slow recovery. She has had three children, and no miscarriages. She states that she had a goitre some twenty-two years ago. She denies veneral disease. She drinks beer, but not to excess.

On October 17, 1903, it was noticed that the patient had a swelling of the right foot that was very painful; it was relieved by massage and bandaging.

On November 3 the right foot again became much swollen and very painful, and at the same time swelling of the thyroid gland, difficulty of deglutition, and pain at the back of the neck were noticed. Subsequently the patient improved, and on December 15, being in good condition and comfortable, she was discharged.

She was readmitted on March 7, 1905, under the care of Dr. Hughes. At this time the diagnosis of myocarditis and nephritis was made, together with adiposis dolorosa. She was seen several times by Dr. Dercum, who confirmed the diagnosis of adiposis dolorosa. She was an extremely large woman, weighing 308 pounds. The superficial fat on the legs was sensitive to palpation. Her general condition was very bad, the pulse rapid, weak, irregular, and of high tension. The respirations were shallow; the expansion was poor. The superficial veins were enlarged. The abdomen was soft and not tender on palpation. The breath sounds were roughened, the expiration prolonged, and a few sonorous rales were audible. The pulmonic second sound of the heart was accentuated. There was a presystolic murmur at the pulmonic area, and the heart's action was irregular. Subsequently the patient suffered markedly from attacks of dyspnœa. Not infrequently she became markedly cyanotic. Gradually she became weaker, and died April 5, 1905.

Autopsy. The autopsy revealed, among other features, marked cardiac hypertrophy with fatty degeneration and chronic nephritis, chronic adhesive pleurisy, œdema and hypostatic congestion of the lungs, and fatty infiltration and congestion of the liver.

The thyroid gland, pituitary body, portions of the fat and skin, and a portion of a radial nerve were removed for examination. The thyroid gland was decidedly larger than normal, particularly the right lobe; the middle lobe was distinctly indurated; the lateral lobes appeared to be normal in consistence. Sections of the right lobe revealed considerable enlargement and dilatation of many of the acini. They were for the most part filled with colloid material. The cubical epithelial lining appeared to be normal, though here and there a tendency to plication of the surface was noted, and in some of the larger acini, small intrusions and plications into the interior of the acini. In certain portions of the sections decided increase of connective tissue was noted. In these areas the acini were relatively small. No changes were noted in the walls of the vessels. Sections of the left lobe revealed an enormous number of greatly dilated acini. Plications of the cubical epithelium were also noted, occurring somewhat more frequently in this lobe than in the right. Sections of the middle lobe revealed changes similar to those already noted, except that there was a relatively larger increase of connective tissue and a smaller number relatively of large acini. In shape and size the pituitary body appeared to be normal. The capsule seemed normal. This appeared also to be the case with the blood-vessels. The glandular portion presented a couple of small areas of round-cell infiltration, but was otherwise normal. In the nervous portion the same peculiar invasion of the glandular cells was found as in Case I. The fatty tissue revealed no striking changes except here and there some apparent increase in the connective tissue trabeculæ. Separate lipomas were not found. Sections of the radial nerve showed no distinct changes. However, here and there some thickening of the endoneurium existed. The perineurium appeared to be normal. Distinct inflammatory changes were not present.

The recognition of adiposis dolorosa as a clinical entity may be said to date from a paper published by Dercum[1] in 1892, under the following title: "Three Cases of a Hitherto Unclassified Affection, Resembling in its Grosser Aspects Obesity, but Associated with Special Nervous Symptoms—Adiposis Dolorosa." This was prefaced by the report of a single case by the same observer in 1888, as "A Subcutaneous Connective Tissue Dystrophy of the Arms and Back, Associated with Symptoms Resembling Myxœdema,"[2] and another by Henry in 1891.[3] Since the appearance of these papers, about fifty cases of Dercum's disease have been reported. many in detail and quite a number briefly and incompletely. In at least two of the reported cases (Fuchs[4] and Cheevers[5]), the diagnosis is questionable, as the patients had neither spontaneous pain nor pain upon manipulation of the adipose deposits.

ETIOLOGY. It has been claimed that adiposis dolorosa may occur in families, but of the two instances reported in support of this statement (Hammond[6] and Cheevers) that of Cheevers may, I think, be ruled out. A family tendency toward obesity, however, is not infrequent. A neuropathic heredity, or a previous personal neuropathic history, has been sometimes noted, but not with sufficient frequency to make it of any special etiological significance. The disease may occur in either sex, females being affected more frequently than males, in the proportion of six to one. The majority of the cases occur between the ages of thirty-five and fifty years, although cases have been reported as commencing at twelve, seventeen, and nineteen years, and one as late as seventy-eight years. Middle aged women who have passed the menopause form the bulk of the cases.

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[1] AMER. JOUR. MED. SCI., 1892, civ, 521.

[2] Univ. Med. Mag., December, 1888.

[3] Jour. Nerv. and Ment. Dis., March, 1891.

[4] Wien. klin Woch., 1905, xviii, 706.

[5] Brit. Med. Jour., 1904, vol. i.

[6] Ibid., vol. ii.

Alcoholism and syphilis have not infrequently formed a background in adiposis dolorosa, and I differ from those who disregard them as possible etiological factors. The toxic and destructive effects of alcohol and syphilis are well known, and the fact that they frequently cause degenerative changes in the ductless glands was emphasized by Lorand.[7]

It is of interest in this connection to recall the case reported by E. W. Taylor, in which the patient developed adiposis dolorosa while convalescing from acute alcoholic neuritis.

SYMPTOMS. Adiposis dolorosa develops gradually in the majority of cases; a few have a more rapid onset; none has developed abruptly. The cardinal symptoms are: (1) Fatty deposit, (2) pain, (3) general asthenia, and (4) psychic phenomena.

Vitaut[8] has divided the cases of adiposis dolorosa into three groups, depending upon the arrangement of the adipose deposit—nodular, circumscribed diffuse, and generalized diffuse. Of the three, the circumscribed diffuse forms the bulk of the cases, generalized diffuse coming next in frequency. Mixed types, or combinations of these forms, are sometimes seen. While the majority of the subjects are extremely obese, many weighing over two hundred pounds and one reported as weighing three hundred pounds, it should be remembered that in some instances the weight is very little, if any, above the average. This I have seen in two cases of the nodular form. The deposits of fat are found most commonly over the trunk, shoulders, arms, and thighs; the forearms and legs being less frequently affected, and the hands and face but rarely.

Pain and tenderness upon manipulation of the adipose deposits are constant symptoms; this is not true, however, of spontaneous pain, which, while the rule, may be entirely absent. Pain upon pressure over the larger nerve trunks is rare, but has been observed in two reported cases. Diminished sensation is, in my experience, a more common symptom than complete anesthesia, while paresthesias are more frequent than either, being present in some form in almost every case. These paresthesias are sensations of numbness, coldness, burning, tingling, or crawling, variously distributed, and often causing the patients much distress.

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[7] An address at a meeting of tne Philadelphia County Medical Society, April 12, 1907

[8] Maladie de Dercum, Lyons, 1901.

The asthenia varies in degree from a tendency to fatigue readily, to extreme weakness or prostration. It is distinctly more pronounced than the fatigue of the average neurasthenic, and is a very constant symptom.

The psychic changes that have been observed in adiposis dolorosa have a wide range, with irritability at one extreme and dementia at the other. When we consider the toxic nature of the disease, it is not surprising that confusion and stupor have each been observed. Mental depression, mental hebetude, melancholia, impairment and loss of memory, have also been noted; one patient was an imbecile, three had "epileptic seizures," two had "convulsions," one became "delusional." The most common mental syndrome is that of irritability associated with depression, some failure of memory, and a marked hypochondriacal tendency.

The tendon reflexes may be normal or increased, but are usually diminished or abolished. One case with loss of the skin reflexes has been recorded by Delecq.

Vasomotor phenomena are next in importance to the so-called cardinal symptoms. Under this heading belong the anidrosis, irregular flushings, cyanosis of the extremities, transitory œdema, and the spontaneous hemorrhages from the nose, stomach, and uterus.

Among trophic changes observed in adiposis dolorosa are ulcerations, the formation of blebs and bullæ, arthritic and bony changes. Other symptoms occasionally found are headache, dyspnœa, tachycardia, insomnia, jaundice, and tremor. Blindness was reported in two cases, circinate retinitis in one case, and hyperemia of the disk in one. Deafness was observed in two cases. The blood changes and urinary findings have both been insignificant.

Organic changes in the central nervous system may be looked upon as coincident rather than being actual symptoms. Hemiplegia and aphasia were present in one case, degeneration of the posterior column of the cord in one case, and signs of lateral tract involvement were marked in an unreported case shown by Dr. Dercum in one of his clinics during the last year at the Jefferson Hospital.

A peculiar tendency of the flesh in this disease is that of bruising upon what would ordinarily be an inadequate cause.

PATHOLOGY. Of the six autopsies reported to date, together with the two herein recorded, the findings may be briefly stated as follows:

CASES I and II.—Dercum: Macroscopic disease of the thyroid, the glands being enlarged and the seat of calcareous infiltration.

CASE III.—Dercum:[9] Irregular atrophy of the thyroid, extensive interstitial neuritis of peripheral nerves in fatty deposits, degeneration in the columns of Goll.

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[9] Jour. Nerv. and Ment. Dis., August, 1900.

CASE IV.—Burr:[10] Glioma of the pituitary body; colloid degeneration with atrophy and absence of secreting cells in many acini of the thyroid gland; interstitial neuritis of terminal filaments; sclerotic ovaries.

CASE V.—Dercum and McCarthy:[11] Adeno-carcinoma of pituitary body, thyroid normal, right suprarenal gland hypertrophied, hemolymph glands, interstitial neuritis, undeveloped testicles.

CASE VI.—Guillain and Alquier:[12] Hypophysis doubled in size with marked increase of connective tissue in the glandular portion and changes suggesting an alveolar carcinoma. Thyroid hypertrophied, with increase in connective tissue stroma.

CASE VII.—Price: Inflammatory changes in thyroid, with marked increase in the interstitial connective tissue, one whole lobe being especially infiltrated, the other showing compensatory hypertrophy. Inflammatory changes in hypophysis, with presence of a condition suggesting alveolar or glandular carcinoma, interstitial and parenchymatous neuritis, sclerotic ovaries.

CASE VIII.—Price: Marked increase in the connective tissue of the thyroid gland, dilation of the acini, with infoldings of the cuboidal epithelial lining. The same changes in the hypophysis as were found in Cases VI and VII, but less marked. No abnormalities of the adipose tissue.

Delecq[13] mentions, as causes of adiposis dolorosa, disease of thyroid, testicle, ovary, and pituitary. Raymond[14] says that the cause is not known and the pathology vague. Von Schroeter looks upon the condition as a "dysthyroidismus." Pineles considers that numerous blood glands are at fault, one of the causes being a hypothyroidismus. Frankenheimer[15] believes adiposis dolorosa to be a dystrophy, and compares it to acromegaly, the former affecting the adipose, and the latter the osseous structures.

While the adipose tissue is affected primarily, changes in other tissue have appeared with sufficient frequency to make the occurrence more than a mere coincidence. Cases with joint involvement have been reported by Dercum,[16] Renon and Heitz, and myself.[17] I have also seen one other case with arthritic changes in the knees and small joints of the hands, producing distinct deformity. A case from the Jefferson Hospital showing imperfectly developed bony structures will soon be placed upon record. There may be, therefore, in adiposis dolorosa, arthritic and osseous as well as adipose changes. Muscular atrophy has been observed in one case only, in association with neuritis of the large nerve trunks.

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[10] Jour. Nerv. and Ment. Dis., 1900, xxvii, 519.

[11] AMER. JOUR. MED. SCI., 1902, p. 994.

[12] Arch. de med. exper. et d'anat. pathol., No. 5, September, 1906.

[13] Presse méd., Paris, 1904, ii, 594 to 596.

[14] Revue neurol. de Paris, 1904, xii, 630 to 632.

[15] Jour. Amer. Med. Assoc., vol. l, No. 13, p. 1012.

[16] Phila. Med. Jour., 1902, x, 1007.

[17] Amer. Med., New Series, vol. ii, No. 5, p. 317.

The thyroid, affected in seven of the eight cases, at once commands our attention. Considered from the standpoint of the symptoms however, there is a peculiar contradiction. The obesity, anidrosis, and improvement following the administration of thyroid extract suggest hypothyroidation, while the flushing, tachycardia, tremor, and often the anxious mental state suggest hyperthyroidation. The term dysthyroidismus would seem, therefore, a better one than hypothyroidismus, as used by Pineles.

We should not, however, in considering the pathogenesis of adiposis dolorosa, neglect the hypophysis. It was found distinctly affected in five of the eight cases, and had been unexamined microscopically in at least two of the remaining three cases. In one instance the thyroid was found to be perfectly normal. Vassale,[18] Ponfick, Kr. Gron,[19] Boyce and Beadles,[20] Langhas, Nufice, Dolego, Bourneville, and others have recorded cases with enlargement of the pituitary in myxœdema. Lediard,[21] Lannois, and Pierre Roy have reported cases of acromegaly with marked hypertrophy of the thyroid.

It has also been found that in animals, when the thyroid is extirpated, the pituitary enlarges. Hutchinson[22] regards the pituitary as a growth centre, which belief is opposed by Guerrini[23] who believes that the secretion of the hypophysis is antitoxic in character, and exerts no trophic influence. Guerrini[24] has proved experimentally that the hypophysis reacts to intoxications, either acute or chronic. Madelung[25] reports a case of injury to the hypophysis followed by enormous obesity, while Berger[26] cites an instance of a tumor behind the chiasm, compressing and flattening an otherwise normal pituitary, with increased obesity, alopecia, and dryness of the skin. Magnus-Levy has found an increased oxidation in acromegaly, resembling that which is present in exophthalmic goitre. Malcolm[27] believes that the "nervous" lobe has a katabolic influence on bony tissue.

It seems, therefore, that sufficient attention has not been given the hypophysis, and I would suggest that etiologically it is of almost as much importance as the thyroid gland. May not the symptom group of adiposis dolorosa result from a primary disease of either of those structures, the other being involved secondarily through their close interrelation?

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[18] Rivista speriment. di Freniatria e med. leg. d. alien. ment., 1902, xxxviii, fasc. 2, 3, p. 25 to 39; Revue Neurologique, June 15, 1903, p. 560.

[19] Norsk Magazine for Laegendenskabess, August, 1894.

[20] Jour. Path. and Bact., i, 233.

[21] Brit. Med. Jour., April 4, 1903, p. 789.

[22] New York Med. Jour., March 12 and April 2, 1898, and July 21 and 28, 1900.

[23] Centralbl. f. allg. Path. u. path. Anat., March 15, 1905, p. 177.

[24] Archivio di fisiologia, an II, fac. III, p. 384 to 386, March, 1905.

[25] Beiträge f. klin. Chirurgie, 1903.

[26] Ztschr. f. klin Med., vol. lxiv, Nos. 5 and 6.

[27] Jour. Physiol., 1904, xxx, 270.

Changes in other structures have been mentioned, especially of the genital organs. Undeveloped testicles have been found in one case and sclerotic ovaries in three cases. Symptoms pointing in this direction are the sterility, loss of sexual power, and hypertrichosis in a female. These changes, however, together with the neuritis of the terminal filaments, appear to be secondary in importance to those in the thyroid and hypophysis.

DIAGNOSIS. A typical case of Dercum's disease should be easy of recognition. The diagnosis should be based chiefly upon the two symptoms—accumulations of adipose tissue, and the presence of pain upon manipulation of these deposits. From multiple neuritis, the diagnosis can be made by the absence of pain and tenderness over the larger nerve trunks, or, when this is present, by the absence of muscular wasting commensurate with the duration and intensity of the pain. In simple lipomatosis there is no pain, and the general symptoms of adiposis dolorosa are absent. In its early stages, the disease has not infrequently been mistaken for rheumatism.

PROGNOSIS. Recovery from adiposis dolorosa is rare, but the disease itself does not directly cause death. Its tendency is usually progressive—often with exacerbations of pain accompanied by increase in size of the adipose deposits. Complete intermissions are rare, but remissions are common.

TREATMENT. The present status of the treatment of adiposis dolorosa leaves much to be desired. At best it is uncertain and unsatisfactory, but by no means hopeless. As in other forms of neuritis, the salicylates are often of value in relieving the pain, and may be advantageously combined with a bromide salt, as the latter tends to lessen the disagreeable effects of the former. Aspirin, being less irritating to the stomach than the ordinary preparations, is often of value. Extract of the thyroid gland, while not a specific, is the most valuable remedy at our command. Several cases have been reported as showing marked improvement following its administration, and Dercum cites one case of cure (the only cure reported) following its use. In my own experience, I have seen five cases distinctly benefited by its administration. It is obvious, however, that the brilliant results obtained in myxœdema, cannot here be expected. The therapy of the pituitary body is at present so indefinite and so little understood, as to make administration of the gland of no practical value.

Potassium iodide should be given whenever there is present a definite history of syphilis, but I have never seen any beneficial results following its administration, even in a case having a specific history.

As the majority of the patients are obese, the heart is likely to be involved in the general adiposity, and may require attention. More general measures, as massage, electricity, rest, etc., frequently add to the comfort of the patient and should never be neglected.

I regret to say, however, that in some cases, fortunately a minority, the symptoms are unrelieved by any of the various remedial measures that have been recommended. As the years bring us a more accurate knowledge of the normal and pathological chemistry of the secretions of the ductless glands, we may hope for more definite therapeutics, and better results in the treatment of this interesting disease.

I desire to express my indebtedness to Dr. F. X. Dercum for the privilege of reporting the cases, and to Dr. W. M. L. Coplin, for many valuable suggestions.

THE CHEMISTRY OF THE URINE IN DIABETES MELLITUS.

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The history of the case which formed the basis of this study is briefly as follows: M. H., a female, aged seventeen years, was admitted to the Montreal General Hospital, in Dr. Finley's service, on January 6, 1908. The family history was negative for diabetes. The personal history was negative until July 28, 1903, when she had an "interval operation" for appendicitis. The urine during this admission had a specific gravity of 1015 and was negative for both albumin and sugar. She was discharged August 19, 1903, the wound having healed "per primam." Two weeks later she developed typhoid fever, during which the wound broke down. On February 16, 1904, she reëntered the hospital to have the sinus closed. The urine was again negative for albumin and sugar and had a specific gravity of 1022. In March, 1906, the appendix wound a second time broke down, and after a prolonged home treatment she was re-admitted on October 6, 1906; the sinus was excised and the edges freshened. The wound closed very slowly, and on her discharge, on November 17, 1906, had not completely healed. The urine was examined three times during October, 1906, but contained no sugar, though the specific gravity was high (1032, 1030, and 1023). The patient felt perfectly well until June, 1907, when she first suffered from weakness, polyuria, and thirst; these symptoms gradually increased in intensity. During November and December, 1907, she noticed an increase in appetite and a tendency to attacks of som-